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INTERNATIONAL APP. NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/09442	21 September 2000	25 September 1999

TITLE OF INVENTION
PIPERAZINE DERIVATIVES AS 5-HT1B ANTAGONISTS

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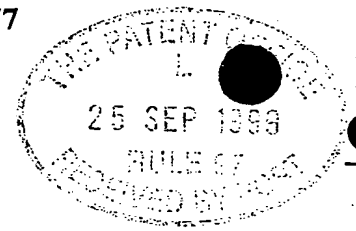

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1. Your reference — DMW/JR/P32422

2. Patent application number
(The Patent Office will fill in his part) — **9922831.4**

3. Full name, address and postcode of the or of each applicant *(underline all surnames)* — SmithKline Beecham plc
New Horizons Court, Brentford, Middx TW8 9EP,
Great Britain

Patents ADP number *(if you know it)* — 57811170001

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention — Novel Compounds

5. Name of your agent *(if you have one)* — CORPORATE INTELLECTUAL PROPERTY

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TWO NEW HORIZONS COURT
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Patents ADP number *(if you know it)* — 58009740004

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11. We request the grant of a patent on the basis of this application

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D M Waters

12. Name and daytime telephone number of person to contact in the United Kingdom: D M Waters 01279 644283

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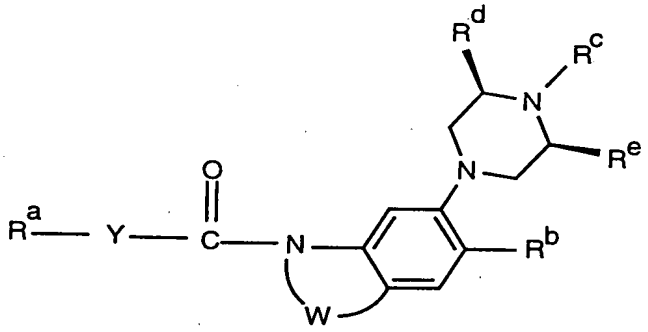
NOVEL COMPOUNDS

The present invention relates to novel piperazine derivatives, processes for their preparation, and pharmaceutical compositions containing them.

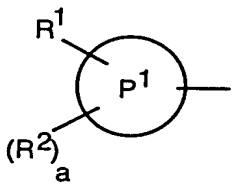
WO 95/06637 discloses a series of piperazine derivatives which are said to possess 5-HT_{1D} receptor antagonist activity. These compounds are alleged to be of use in the treatment of various CNS disorders such as depression. The human 5-HT_{1D} receptor is now known to be encoded by two distinct genes initially designated 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ and subsequently redesignated as 5-HT_{1D} and 5-HT_{1B} respectively (P.R Hartig et al Trends in Pharmacological Science, 1996, **17**, 103 - 105). WO 98/50538 and WO 98/47885 disclose a series of piperazine derivatives that are said to exhibit combined 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptor antagonist activity.

A structurally distinct class of compounds has now been found to exhibit 5-HT_{1B} receptor activity. It is expected that such compounds will be useful for the treatment and prophylaxis of various CNS disorders. In a first aspect, the present invention therefore provides a compound of formula (I) or a salt thereof:



(I)

in which R^a is a group of formula (i)



(i)

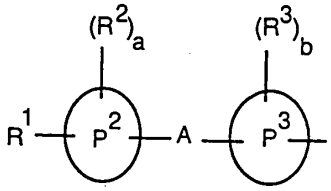
wherein P^1 is phenyl, naphthyl or heteroaryl;

R^1 is hydrogen, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, COC_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, hydroxyC_{1-6}alkyl, nitro, CF_3, cyano, SR^9, SOR^9, SO_2R^9, $SO_2NR^{10}R^{11}$, CO_2R^{10}, $CONR^{10}R^{11}$, $OCONR^{10}R^{11}$, $NR^{10}R^{11}$, $NR^{10}CO_2R^{11}$, $NR^{10}CONR^{10}R^{11}$, CR^{10}=NOR^{11} where R^9, R^{10} and R^{11} are independently hydrogen or C_{1-6}alkyl;

R^2 is halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkenyl, C_{1-6}alkoxy, COC_{1-6}alkyl, hydroxy, nitro, CF_3, cyano, CO_2R^{10}, $CONR^{10}R^{11}$, $NR^{10}R^{11}$ where R^{10} and R^{11} are as defined above;

a is 0, 1, 2 or 3;

or R^a is a group of formula (ii)



(ii)

wherein

P^2 is phenyl, naphthyl, heteroaryl or a 5- to 7- membered heterocyclic ring;

P^3 is phenyl, naphthyl or heteroaryl;

A is a bond or oxygen, carbonyl, CH_2 or NR^4 where R^4 is hydrogen or C_{1-6}alkyl;

R^1 is as defined above for formula (i) or R^1 is heteroaryl optionally substituted by C_{1-6}alkyl, halogen or COC_{1-6}alkyl;

R^2 and R^3 are independently halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, COC_{1-6}alkyl, hydroxy, nitro, CF_3, cyano, CO_2R^{10}, $CONR^{10}R^{11}$, $NR^{10}R^{11}$ where R^{10} and R^{11} are as defined above;

and a and b are independently 0, 1, 2 or 3;

Y is a bond, CH_2, O or NR^5 where R^5 is hydrogen or C_{1-6}alkyl;

W is $(CR^{16}R^{17})_t$ where t is 2, 3 or 4 and R^{16} and R^{17} are independently hydrogen or C_{1-6}alkyl or W is a group CH=CH;

R^b is hydrogen, halogen, hydroxy, C_{1-6}alkyl, CF_3 or C_{1-6}alkoxy;

R^c is hydrogen or C_{1-6}alkyl.

R^d and R^e are both independently C_{1-4}alkyl.

Alkyl groups, whether alone or as part of another group, may be straight chain or branched. The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine.

Where used herein the term naphthyl is intended, unless otherwise stated, to denote both naphth-1-yl and naphth-2-yl groups.

The term "heteroaryl" is intended to mean an aromatic or a benzofused aromatic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur. Suitable examples of such aromatic rings include thienyl, furyl, pyrrolyl, triazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrimidyl, pyridazinyl, pyrazinyl and pyridyl. Suitable examples of such benzofused aromatic rings include quinolinyl, isoquinolinyl, indolyl, benzofuryl and benzothienyl.

The term "5 - 7 membered heterocyclic ring" is used herein to mean a non aromatic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur. Suitable examples of such non aromatic rings include piperidinyl, piperazinyl, pyrrolidinyl, 2-oxo pyrrolidinyl and morpholinyl.

The heteroaryl and 5 - 7 membered heterocyclic rings, as described above, can be linked to the remainder of the molecule via a carbon atom or, when present, a suitable nitrogen atom.

Within the definition of R^a formula (i)

When P^1 is heteroaryl a preferred example is quinolinyl. Preferably P^1 is phenyl or naphthyl.

R^1 is preferably hydrogen, nitro, halogen (particularly chloro) or a C_{1-6}alkyl group (particularly methyl).

When a is not 0, R^2 is preferably halogen (particularly chloro) or a C_{1-6}alkyl group (particularly methyl). When a is 2 or 3 the groups R^2 may be the same or different.

a is preferably 0, 1 or 2, most preferably 0 or 1.

Within the definition of R^a formula (ii)

A is preferably a bond or oxygen, most preferably a bond.

When P^3 is heteroaryl a preferred example is quinolinyl (particularly 4-quinolinyl). P^3 is preferably phenyl or naphthyl. A preferred substitution arrangement for naphthyl groups is 1,4 or 1,5, that is to say, a naphth-1-yl group in which the group A is attached at the 4 or 5 position respectively.

P^2 is preferably a heteroaryl group such as pyridyl, oxadiazolyl or oxazolyl or a 5 – 7 membered heterocycle such as piperidinyl.

When R^1 is heteroaryl a preferred group is oxadiazolyl. A preferred optional substituent for such a group is C_{1-6}alkyl (particularly methyl).

When a and/or b is not 0, R^2 and/or R^3 are each preferably halogen (particularly chloro), or a C_{1-6}alkyl group (particularly methyl). When a and/or b is 2 or 3 the groups R^2 and/or R^3 may be the same or different.

a and b are each preferably 0, 1 or 2, most preferably 0 or 1.

The most preferred compounds of formula (ii) are those in which P^2 is pyridyl, (particularly 2-pyridyl) and P^3 is naphthyl.

Y is preferably a bond, CH_2 or a NH group.

It will be appreciated that when W is a group CH=CH an indole ring is formed. Within the definition of the group W, the groups R^{16} and R^{17} are each preferably hydrogen and t is preferably 2 or 3, most preferably 2.

R^b is preferably a C_{1-6}alkoxy group, most preferably methoxy.

R^c is preferably a C_{1-6}alkyl group, most preferably methyl.

The groups R^d and R^e can be the same or different. A preferred C_{1-4}alkyl group is methyl.

Particularly preferred compounds according to the invention include:-

cis-5-methoxy-1-[4-(6-methylpyridin-2-yl)naphth-1-ylcarbonyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline,

cis-5-methoxy-1-[5-(6-methylpyridin-2-yl)naphth-1-ylcarbonyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline,

cis-5-methoxy-1-[5-(5-methyloxazol-2-yl)naphth-1-ylcarbonyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline,

cis-1-(2,3-dichlorobenzoyl)-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline,

cis-5-methoxy-1-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carbonyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline,

cis-5-methoxy-1-[4-(6-methylpyridin-2-yl)naphth-1-ylaminocarbonyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline,
cis-5-methoxy-1-[5-(6-methylpyridin-2-yl)naphth-1-ylaminocarbonyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline,
cis-5-methoxy-1-[5-(5-methyloxazol-2-yl)naphth-1-ylaminocarbonyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline,
cis-1-(2,3-dichlorophenylaminocarbonyl)-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline,
cis-5-methoxy-1-[(3-nitrophenyl)acetyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline,
cis-5-methoxy-1-[4-(1-methylpiperidin-4-yl)naphth-1-ylcarbonyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline,
cis-6-(3,5-dimethylpiperazin-1-yl)-5-methoxy-1-[4-(6-methylpyridin-2-yl)naphth-1-ylcarbonyl]indoline
or a pharmaceutically acceptable salts thereof.

Preferred salts of the compounds of formula (I) are pharmaceutically acceptable salts. These include acid addition salts such as hydrochlorides, hydrobromides, phosphates, acetates, fumarates, maleates, tartrates, citrates, oxalates, methanesulphonates and p-toluenesulphonates.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and the mixtures thereof including racemates.

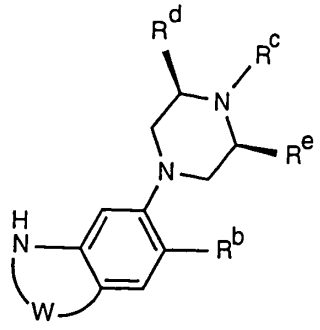
Compounds of the invention can be prepared using procedures known in the art. In a further aspect the present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof which comprises:

(a) Y is NH, coupling a compound of formula (II):

$$R^a\text{–N-(C = O)}$$

(II)

in which R^a are as defined in formula (I) or a protected derivative thereof with a compound of formula (III):



(III)

in which W, R^b and R^c, R^d and R^e are as defined in formula (I), or a protected derivative thereof; or

(b) where Y is NR^5, reacting a compound of formula (IV)

$$R^a\text{-}NR^5H$$

(IV)

in which R^a and R^5 are as defined in formula (I) with a compound of formula (III) together with an appropriate urea forming agent;

(c) where Y is a bond, CH_2 or O, reacting a compound of formula (V)

$$R^a\text{-}Y\text{-}(C{=}O)\text{-}L^2$$

(V)

in which R^a is as defined in formula (I) and L^2 is an appropriate leaving group, with a compound of formula (III);

and optionally thereafter

- removing any protecting groups,
- converting a compound of formula (I) into another compound of formula (I),
- forming a pharmaceutically acceptable salt.

The reaction in process (a) is conveniently effected in an organic solvent such as dichloromethane.

In process (b) the urea forming agent can be carbonyl diimidazole, triphosgene or phosgene, and carried out in an inert organic solvent such as dimethylformamide, tetrahydrofuran or dichloromethane at ambient or elevated temperature in the presence of a base such as triethylamine or pyridine.

In process (c) the leaving group L^2 may be a halogen e.g. chloro group and the reaction may be carried out in an inert organic solvent such as tetrahydrofuran or dichloromethane at ambient or elevated temperature in the presence of a base such as triethylamine or pyridine.

Compounds of formula (I) can be converted into further compounds of formula (I) using standard techniques. For example, in the case wherein R^c is hydrogen, it is possible to introduce a C_{1-6}alkyl group by conventional alkylation using 1 molar equivalent of a C_{1-6}alkyl halide and 1 molar equivalent of a suitable base in an inert solvent.

Intermediate compounds of formula (II), (III), (IV) and (V) can be prepared using standard procedures described herein or by methods known to those skilled in the art.

It will be appreciated to those skilled in the art that it may be necessary to protect certain reactive substituents during some of the above procedures. Standard protection and deprotection techniques can be used. For example, primary amines can be protected as phthalimide, benzyl, benzyloxycarbonyl or trityl derivatives. These groups can be removed by conventional procedures well known in the art.

Carboxylic acid groups can be protected as esters. Aldehyde or ketone groups can be protected as acetals, ketals, thioacetals or thioketals. Deprotection is achieved using standard conditions.

The involvement of serotonin (5-hydroxytryptamine; 5HT) receptors in a number of pharmacological effects has been reviewed by R. A. Glennon in "Serotonin Receptors: Clinical Implications", Neuroscience and Behavioural Reviews, 1990, 14, 35 and by L.O.Wilkinson and C.T. Dourish in "Serotonin Receptor Subtypes : Basic and Clinical Aspects" S. Peroutka Ed., John Wiley and Sons, New York, 1991 p.147.

Serotonin receptors have been implicated in pharmacological effects such as mood disorders including depression, seasonal affective disorder and dysthymia, anxiety disorders, including generalised anxiety, panic disorder, agoraphobia, social phobia, obsessive compulsive disorder and post-traumatic stress disorder; memory disorders, including dementia, amnesic disorders and age-associated memory impairment; disorders

of eating behaviours, including anorexia nervosa and bulimia nervosa, sleep disorders (including disturbances of Circadian rhythm), motor disorders such as Parkinson's disease, dementia in Parkinson's disease, neuroleptic-induced Parkinsonism and tardive dyskinesias, as well as other psychiatric disorders. Serotonin receptor ligands have been shown to be of use in the treatment of emesis and nausea and may also be of use in endocrine disorders such as hyperlactinaemia, vasospasm (particularly in the cerebral vasculature), cerebellar ataxia and hypertension, as well as disorders of the gastrointestinal tract where changes in motility and secretion are involved. They may also be of use in the treatment of sexual dysfunction and hypothermia.

Ligands with high affinity for the 5-HT_1 receptors are well recognised as having therapeutic utility for the treatment of the above conditions. It has been suggested that a selective 5-HT_{1B} receptor antagonist should act as a fast onset antidepressant (P Blier Trends Pharmacol. Sci. 1994, 15, 220).

The present invention also provides a compound of general formula (I) or a pharmacologically acceptable salt or solvate thereof for use in the treatment of the aforementioned disorders.

In a further aspect the invention provides a method of treating the aforementioned disorders which comprises administering an effective amount to a patient in need of such treatment of a compound of general formula (I) or a pharmaceutically acceptable salt or solvate thereof.

In particular the invention provides a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in the treatment or prophylaxis of depression.

The affinities of the compounds of this invention for the 5-HT_{1B} receptor can be determined by the following radioligand binding assay. CHO cells expressing 5-HT_{1B} receptors (4×10^7 cells/ml) are homogenised in Tris buffer Mg^{2+} and stored in 1.0 ml aliquots. 0.4 ml of a cell suspension is incubated with [^{3}H]-5-HT (4nM) in Tris Mg HCl buffer (pH 7.7) and test drug, at 37°C for 45 minutes. Each test drug is tested at 10 concentrations (0.01 mM to 0.3 nM final concentration), with non-specific binding defined using 0.01 mM 5-HT. The total assay volume is 0.5 ml. Incubation is stopped by rapid filtration using a Tomtec Harvester (filters pre-washed in 0.3% polyethylenimine) and radioactivity measured by Topcount scintillation counting. pKi values are calculated from the IC_{50} generated by an iterative least squares curve fitting programme.

The intrinsic activity of the compounds of this invention can be determined according to the following procedure. CHO cell membranes stably expressing human 5-HT_{1B} receptors are homogenised in HEPES/EDTA buffer and stored in 1ml aliquots, and

[^{35}S]GTPγS binding studies are carried out essentially as described by Lazareno *et al.*, (Life Sci., 1993, **52**, 449) with some minor modifications. Membranes from 10^6 cells are pre-incubated at 30°C for 30 min in 20 mM HEPES buffer (pH 7.4) in the presence of $MgCl_2$ (3 mM), NaCl (100 mM), GDP (10 μM) and ascorbate (0.2 mM), with or without compounds. The reaction is started by the addition of 50 μl of [^{35}S]GTPγS (100pm, assay concentration) followed by a further 30 minutes incubation at 30°C. Non-specific binding was determined using non-radiolabelled GTPγS (20 μM) added prior to the membranes. The reaction is terminated by rapid filtration through Whatman GF/B grade filters followed by 5 x 1 ml washes with ice cold HEPES (20 mM) /$MgCl_2$ (3 mM) buffer. Radioactivity is measured using liquid scintillation spectrometry. This procedure is hereafter referred to as the [^{35}S]GTPγS functional assay.

The compounds of formula (I) show high affinity for the 5-HT_{1B} receptor. It has been found, using the [^{35}S]GTPγS functional assay, that certain compounds of formula (I) show varying levels of intrinsic efficacy, which is defined by a scale ranging from 1.0 to 0 (1 defines the maximum response elicited by the agonist 5-HT, 0 defines antagonism). The difficulties in describing intrinsic activity of drugs acting at G protein coupled receptors is recognised in the art (Hoyer and Boddeke, Trends in Pharmacological Sciences, July 1993, [Vol. 14], page 270-275). We believe that however these ligands are classified according to this functional assay, the compounds of this invention will be useful antidepressants *in vivo*. It is believed that the preferred compounds of this invention will display 5-HT_{1B} antagonist activity *in vivo* and that such compounds will have a rapid onset of action. A rapid onset of action is particularly advantageous for antidepressant compounds: by 'rapid onset of action' we mean that a therapeutic response is seen within 7 days from first administration of the compound, as opposed to a period of about 21 days or more which is typical of SSRI's, tricyclic antidepressants and buspirone.

Compounds of formula (I) which have an intrinsic activity of 0.5 or less in the [^{35}S]GTPγS functional assay are particularly preferred, as these compounds are more likely to be full antagonists *in vivo*.

It will be appreciated by those skilled in the art that the compounds according to the invention may advantageously be used in conjunction with one or more other therapeutic agents, for instance, different antidepressant agents.

The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number of weeks or months.

The following Examples illustrate the preparation of compounds of the invention.

Description 1

1-Acetyl-6-bromo-5-methoxyindoline (D1)

A stirred solution of 1-acetyl-6-bromoindolin-5-ol (Tetrahedron 1973, 29(8), 1115, 40g, 0.15mole) in DMF (500ml) was treated with K_2CO_3 (61g, 0.45mole) and iodomethane (11.7ml, 0.19mole) and maintained at room temperature for 20h, then concentrated under vacuum to 200ml. The residue was treated with water (200ml) and the precipitate filtered off, dried and re-crystallised from EtOAc to afford the title compound as a white solid (35.7g, 85%).

Description 2

***cis*-1-Acetyl-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline (D2)**

A mixture of palladium (II) acetate (500mg), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (2.0g) and cesium carbonate (10.3g) in dry degassed 1,4-dioxane (120ml) under argon was sonicated at 28°C for 0.5h producing a pink heterogeneous mixture. This was treated with 1-acetyl-6-bromo-5-methoxyindoline (D1, 6.0g, 22mmole) followed by *cis*-1,2,6-trimethylpiperazine (J. Med. Chem. 1968, 11, 592; 4.8g, 38mmole) and heated with good stirring at reflux for 70h. The mixture was allowed to cool, then concentrated under vacuum. The residue was treated with water and extracted with EtOAc. The organic solution was then extracted with 1M HCl acid and the extract was basified by addition of K_2CO_3 and extracted with EtOAc. The extract was dried (Na_2SO_4) and concentrated under vacuum to leave an orange solid, which was chromatographed on silica gel eluting with 0-10% MeOH/DCM to afford the required product as a pale yellow solid (1.6g, 23%).

Description 3

***cis*-5-Methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline (D3)**

A stirred solution of *cis*-1-acetyl-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline (D2, 1.6g, 5mmole) in 2M HCl acid (50ml) was heated under reflux for 2h, then the solution was allowed to cool, basified with K_2CO_3 and extracted with DCM. The extract was dried (Na_2SO_4) and concentrated under vacuum to afford the title compound as a pale orange solid (1.4g, 100%).

Description 4

***cis*-1-Acetyl-6-(4-benzyl-3,5-dimethylpiperazin-1-yl)-5-methoxyindoline (D4)**

The title compound was prepared from *cis*-1-benzyl-2,6-dimethylpiperazine (Org. Prep. Proc. 1976, 8, 19) and 1-acetyl-6-bromo-5-methoxyindoline (D1) using a similar procedure to Description 2 (43%).

Description 5

***cis*-6-(4-Benzyl-3,5-dimethylpiperazin-1-yl)-5-methoxyindoline (D5)**

The title compound was prepared from *cis*-1-acetyl-6-(4-benzyl-3,5-dimethylpiperazin-1-yl)-5-methoxyindoline (D4) by a similar procedure to Description 3 as a beige solid (100%)

Description 6

***cis*-6-(4-Benzyl-3,5-dimethylpiperazin-1-yl)-5-methoxy-1-[4-(6-methylpyridin-2-yl)naphth-1-ylcarbonyl]indoline (D6)**

The title compound was prepared from *cis*-6-(4-benzyl-3,5-dimethylpiperazin-1-yl)-5-methoxyindoline (D5) and 4-(6-methylpyridin-2-yl)-1-naphthoic acid following a similar procedure to Example 1 as a white solid (85%).

Description 7

Methyl 4-(trimethylstannyl)-1-naphthoate (D7)

A stirred solution of methyl 4-bromo-1-naphthoate (Collect. Czech. Chem. Commun. 1997, 62(11), 1737, 7.3g, 28mmole) in degassed toluene (300ml) was treated with hexamethylditin (10g, 31mmole) and tetrakis(triphenylphosphine)palladium(0) (720mg) and heated at reflux under argon for 3h. On cooling, the mixture was filtered through celite, concentrated under vacuum and the residue chromatographed on silica gel eluting with 0-3% ether/60-80 petrol to afford the title compound as a colourless oil (9.06g, 94%).

Description 8

Methyl 4-(pyridin-4-yl)-1-naphthoate (D8)

A stirred solution of methyl 4-(trimethylstannyl)-1-naphthoate (D7, 9.06g, 26mmole) in dry degassed DMF (150ml) was treated with copper (I) iodide (495mg, 2.6mmole), dichlorobis(triphenylphosphine)palladium(II) (1.52g, 2.2mmole) and 4-bromopyridine (prepared by suspending the HCl salt (6.07g, 31mmole) in 40% KOH solution, extracting with toluene and adding the dried toluene solution to the reaction). The mixture was heated at reflux under argon for 5h and allowed to cool before removing the DMF under vacuum. The residue was partitioned between EtOAc and 10% $NaHCO_3$ solution and the organics dried (Na_2SO_4) and chromatographed on silica gel eluting with EtOAc to afford the title compound as a white solid (4.1 g, 60%).

Description 9

Methyl 4-(1-methylpiperidin-4-yl)-1-naphthoate (D9)

A stirred solution of methyl-4-(pyridin-4-yl)-1-naphthoate (D8, 2.0 g, 7.6 mmole) in acetone (20 ml) was treated with methyl iodide (1.0ml, 15mmole), stirred for 0.5h and then allowed to stand at room temperature for 2 days. The resultant yellow precipitate was filtered off to afford the pyridinium salt as yellow crystals (2.87g). This was dissolved in EtOH (30 ml) and DMF (90 ml) and was hydrogenated at 50 psi and room temp over PtO_2 for 24h. The mixture was filtered through celite and the filtrate concentrated under vacuum to a brown oil, which was partitioned between DCM and 10% $NaHCO_3$ solution and the organic solution separated, dried (Na_2SO_4) and concentrated under vacuum to afford the title compound as a brown oil (1.82 g, 91%).

Example 1

***cis*-5-Methoxy-1-[4-(6-methylpyridin-2-yl)naphth-1-ylcarbonyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E1)**

A suspension of 4-(6-methylpyridin-2-yl)-1-naphthoic acid (D91 in WO 98/50398, 92mg, 0.35 mmole) in DCM (10ml) was treated with oxalyl chloride (75mg, 0.60mmole) and stirred at room temperature for 18h, then concentrated under vacuum to leave the acid chloride as a yellow solid. This was redissolved in DCM (10ml) and added to a stirred solution of *cis*-5-methoxy 6-(3,4,5-trimethylpiperidin-1-yl)indoline (D3, 100mg, 0.38mmole) and pyridine (47mg, 0.60mmole) in DCM (10ml) at 0°C under argon. The reaction mixture was allowed to warm to room temperature and stir for 3h, then treated with polystyrene bound methylisocyanate (100mg of 1.2mmole/g) and stirred for 18h, then filtered through kieselguhr. The filtrate was washed with 10% Na_2CO_3 solution, dried (Na_2SO_4), concentrated under vacuum and the residue purified by chromatography

on basic alumina eluting with EtOAc to afford the title compound as a yellow solid (110mg, 60%).

^{1}H NMR (250MHz, $CDCl_3$) - spectrum highly complex due to hindered rotation with most peaks doubled up. Major peaks discernible: δ 6.75 & 6.68 (2xs, together 1H = 4H), 3.87 & 3.75 (2xs, together 3H = OMe), 3.16 & 3.00 (2xt, together 2H, = indoline CH_2), 2.69 (s, 3H, = pyridyl Me), 2.34 & 2.12 (2xs, together 3H, = piperazine N-Me), 1.17 & 0.85 & 0.79 (3xd, together 6H, = 3 and 5-piperazine Me). MH^+ 521.

The following compounds were prepared by a similar method to that of Example 1 using *cis*-5-methoxy 6-(3,4,5-trimethylpiperidin-1-yl)indoline and an appropriate acid chloride derivative:

Example	MH^+
***cis*-5-methoxy-1-[5-(6-methylpyridin-2-yl)naphth-1-ylcarbonyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E2)**	521
***cis*-5-methoxy-1-[5-(5-methyloxazol-2-yl)naphth-1-ylcarbonyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E3)**	511
***cis*-1-(2,3-dichlorobenzoyl)-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E4)**	448/450
***cis*-5-methoxy-1-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carbonyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E5)**	552

Example 6

***cis*-5-Methoxy-1-[4-(6-methylpyridin-2-yl)naphth-1-ylaminocarbonyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E6)**

A stirred mixture of 4-(6-methylpyridin-2-yl)-1-naphthoic acid (D91 in WO 98/50358 , 87mg, 0.33mmole), triethylamine (40mg, 0.40mmole) and diphenylphosphoryl azide (96mg, 0.35mmole) in toluene was heated at reflux under argon for 0.5h, then allowed to cool to room temperature and treated with a solution of *cis*-5-methoxy 6-(3,4,5-trimethylpiperidin-1-yl)indoline (D3, 70mg, 0.25mmole) in DCM (10ml). The mixture was stirred at room temperature for 4h, then treated with polystyrene bound trisamine (80mg of 3.6mmole/g) and polystyrene bound methylisocyanate (60mg of 1.2mmole/g) and stirred at room temperature for 70h, then filtered through kieselguhr. The filtrate was washed with 10% Na_2CO_3 solution, dried (Na_2SO_4), concentrated under vacuum and

purified by chromatography on basic alumina eluting with EtOAc, followed by trituration with Et_2O to afford the title compound as a yellow solid (70mg, 52%).
^1H NMR (250MHz, $CDCl_3$) δ 8.13 (d, 1H), 7.98 (d, 1H), 7.90 (d, 1H), 7.78-7.70 (m, 2H), 7.61 (d, 1H), 7.60-7.45 (m, 2H), 7.34 (d, 1H), 7.21 (d, 1H), 6.76 (s, 1H), 6.75 (s, 1H), 4.25 (t, 2H), 3.85 (s, 3H), 3.38-3.21 (m, 4H), 2.67 (s, 3H), 2.55-2.40 (m, 4H), 2.30 (s, 3H), 1.09 (d, 6H). MH^+ 536.

The following compounds were prepared by a similar method to that of Example 6.

Example	MH^+
***cis*-5-methoxy-1-[5-(6-methylpyridin-2-yl)naphth-1-ylaminocarbonyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E7)**	536
***cis*-5-methoxy-1-[5-(5-methyloxazol-2-yl)naphth-1-ylaminocarbonyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E8)**	526
***cis*-1-(2,3-dichlorophenylaminocarbonyl)-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E9)**	465/465

Example 10

***cis*-5-Methoxy-1-[(3-nitrophenyl)acetyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E10)**

The title compound was prepared from 3-nitrophenylacetic acid and *cis*-5-methoxy 6-(3,4,5-trimethylpiperidin-1-yl)indoline (D3) using a similar procedure to Example 1 as an orange solid (21%).
^1H NMR (250MHz, $CDCl_3$) δ 8.20-8.12 (m, 2H), 7.91 (s, 1H), 7.68 (d, 1H), 7.60-7.50 (m, 1H), 6.72 (s, 1H), 4.15 (t, 2H), 3.88 (s, 2H), 3.84 (s, 3H), 3.37-3.25 (m, 2H), 3.20 (t, 2H), 2.55-2.40 (m, 4H), 2.30 (s, 3H), 1.10 (d, 6H). MH^+ 439.

Example 11

***cis*-5-Methoxy-1-[4-(1-methylpiperidin-4-yl)naphth-1-ylcarbonyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E11)**

A stirred solution of *cis*-5-methoxy 6-(3,4,5-trimethylpiperidin-1-yl)indoline (D3, 58mg, 0.21mmole) in toluene (5ml) under argon was treated with a 2M trimethylaluminium in toluene (0.13ml, 0.25mmole), then stirred at room temperature for 0.75h. A solution of methyl 4-(1-methylpiperidin-4-yl)-1-naphthoate (D9, 60mg, 0.21mmole) in toluene (5ml) was added and the mixture was heated under reflux for 3.5h, then allowed to cool to room temperature. The mixture was added to a 5g silica gel column and eluted with 0-10%

MeOH/DCM to afford a yellow oil. This was further purified by preparative plate TLC on silica gel eluting with 9:1:0.1 DCM/MeOH/0.88 NH_3 to afford the title compound as a white solid (39mg, 35%). MH^+ 527.

Example 12

***cis*-6-(3,5-Dimethylpiperazin-1-yl)-5-methoxy-1-[4-(6-methylpyridin-2-yl)naphth-1-ylcarbonyl]indoline (E12)**

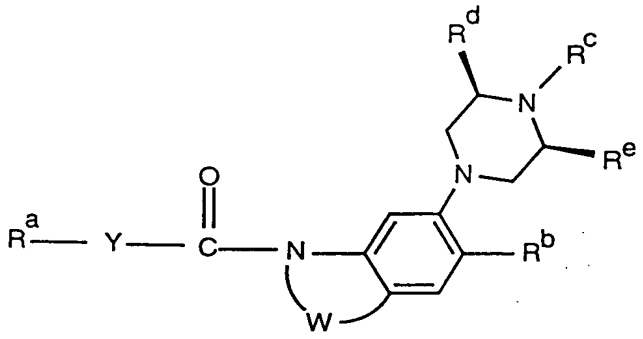
A solution of cis-6-(4-benzyl-3,5-dimethylpiperazin-1-yl)-5-methoxy-1-[4-(6-methylpyridin-2-yl)naphth-1-ylcarbonyl]indoline (D6, 380mg, 0.64mmole) in EtOH (50ml) and THF (50ml) was treated with 10% Pd-C (300mg) and stirred under a hydrogen atmosphere at ambient temperature and pressure for 70h. The mixture was filtered through kieselguhr and concentrated under vacuum. The residue was purified by chromatography on basic alumina eluting with EtOAc followed by crystallisation from Et_2O to afford the title compound as a yellow solid (320mg, 98%). MH^+ 507.

Pharmacological Data

All examples had pKi values >7.3 at 5-HT_{1B} receptors and examples 1, 3, 6, 9, 10, 11 had pKi values >8.0 at 5-HT_{1B} receptors.

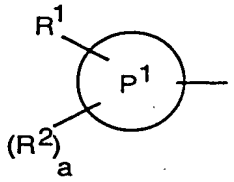
CLAIMS

1. A compound of formula (I) or a salt thereof:



(I)

in which R^a is a group of formula (i)



(i)

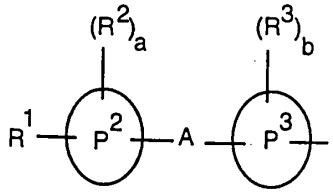
wherein P^1 is phenyl, naphthyl or heteroaryl;

R^1 is hydrogen, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, COC_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, hydroxyC_{1-6}alkyl, nitro, CF_3, cyano, SR^9, SOR^9, SO_2R^9, $SO_2NR^{10}R^{11}$, CO_2R^{10}, $CONR^{10}R^{11}$, $OCONR^{10}R^{11}$, $NR^{10}R^{11}$, $NR^{10}CO_2R^{11}$, $NR^{10}CONR^{10}R^{11}$, CR^{10}=NOR^{11} where R^9, R^{10} and R^{11} are independently hydrogen or C_{1-6}alkyl;

R^2 is halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkenyl, C_{1-6}alkoxy, COC_{1-6}alkyl, hydroxy, nitro, CF_3, cyano, CO_2R^{10}, $CONR^{10}R^{11}$, $NR^{10}R^{11}$ where R^{10} and R^{11} are as defined above;

a is 0, 1, 2 or 3;

or R^a is a group of formula (ii)



(ii)

wherein

P^2 is phenyl, naphthyl, heteroaryl or a 5- to 7- membered heterocyclic ring;

P^3 is phenyl, naphthyl or heteroaryl;

A is a bond or oxygen, carbonyl, CH_2 or NR^4 where R^4 is hydrogen or C_{1-6}alkyl;

R^1 is as defined above for formula (i) or R^1 is heteroaryl optionally substituted by C_{1-6}alkyl, halogen or COC_{1-6}alkyl;

R^2 and R^3 are independently halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, COC_{1-6}alkyl, hydroxy, nitro, CF_3, cyano, CO_2R^{10}, $CONR^{10}R^{11}$, $NR^{10}R^{11}$ where R^{10} and R^{11} are as defined above;

and a and b are independently 0, 1, 2 or 3;

Y is a bond, CH_2, O or NR^5 where R^5 is hydrogen or C_{1-6}alkyl;

W is $(CR^{16}R^{17})_t$ where t is 2, 3 or 4 and R^{16} and R^{17} are independently hydrogen or C_{1-6}alkyl or W is a group CH=CH;

R^b is hydrogen, halogen, hydroxy, C_{1-6}alkyl, CF_3 or C_{1-6}alkoxy;

R^c is hydrogen or C_{1-6}alkyl;

R^d and R^e are both independently C_{1-4}alkyl.

2. A compound according to claim 1 in which R^a is a group of formula (i) wherein P^1 is phenyl or naphthyl.

3. A compound according to claim 1 in which R^a is a group of formula (ii) wherein P^3 is phenyl or naphthyl.

4. A compound according to claim 3 in which P^2 is pyridyl.

5. A compound according to any of the preceding claims in which R^d and R^e are both methyl

6. A compound according to claim 1 which is:

cis-5-methoxy-1-[4-(6-methylpyridin-2-yl)naphth-1-ylcarbonyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline,

cis-5-methoxy-1-[5-(6-methylpyridin-2-yl)naphth-1-ylcarbonyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline,

cis-5-methoxy-1-[5-(5-methyloxazol-2-yl)naphth-1-ylcarbonyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline,

cis-1-(2,3-dichlorobenzoyl)-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline,

cis-5-methoxy-1-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carbonyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline,

cis-5-methoxy-1-[4-(6-methylpyridin-2-yl)naphth-1-ylaminocarbonyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline,

cis-5-methoxy-1-[5-(6-methylpyridin-2-yl)naphth-1-ylaminocarbonyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline,

cis-5-methoxy-1-[5-(5-methyloxazol-2-yl)naphth-1-ylaminocarbonyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline,

cis-1-(2,3-dichlorophenylaminocarbonyl)-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline,

cis-5-methoxy-1-[(3-nitrophenyl)acetyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline,

cis-5-methoxy-1-[4-(1-methylpiperidin-4-yl)naphth-1-ylcarbonyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline,

cis-6-(3,5-dimethylpiperazin-1-yl)-5-methoxy-1-[4-(6-methylpyridin-2-yl)naphth-1-ylcarbonyl]indoline

or a pharmaceutically acceptable salts thereof.

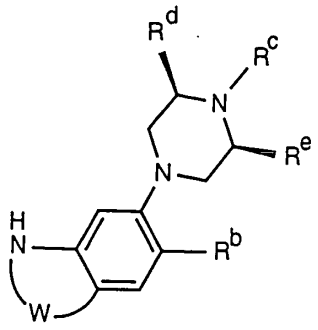
7. A process for the preparation of a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof which comprises:

(a) Y is NH, coupling a compound of formula (II):

$$R^a\text{–N-(C = O)}$$

(II)

in which R^a are as defined in formula (I) or a protected derivative thereof with a compound of formula (III):



(III)

in which W, R^b and R^c, R^d and R^e are as defined in formula (I), or a protected derivative thereof; or

(b) where Y is NR^5, reacting a compound of formula (IV)

$$R^a\text{-}NR^5H$$

(IV)

in which R^a and R^5 are as defined in formula (I) with a compound of formula (III) together with an appropriate urea forming agent;

(c) where Y is a bond, CH_2 or O, reacting a compound of formula (V)

$$R^a\text{-}Y\text{-}(C{=}O)\text{-}L^2$$

(V)

in which R^a is as defined in formula (I) and L^2 is an appropriate leaving group, with a compound of formula (III);

and optionally thereafter:

- removing any protecting groups,
- converting a compound of formula (I) into another compound of formula (I),
- forming a pharmaceutically acceptable salt.

8. A compound according to any of claims 1 to 6 for use in therapy.

9. A compound according to any one of claims 1 to 6 for use in the treatment of anxiety and/or depression.

10. A pharmaceutical composition which comprises a compound according to any of claims 1 to 6 and a pharmaceutically acceptable carrier.

ABSTRACT

Novel piperazine derivatives, processes for their preparation, and pharmaceutical compositions containing them